provide proper dependency. An appendix with the amended and added claims is provided for the Examiner's convenience. No new matter was added by these amendments.

The amendments to the specification were to correct a typographical errors. Support for the chromosomal localization of the z219c gene on chromosome 3, at 3p21.1-p13, is shown in Example 3 on page 86. No new matter was added by these amendments.

A. Rejections Addressed from June 21 Office Action (OA)

(1) Rejection of Claims 5-9, and 15 under 35 U.S.C. §112, Second Paragraph

Claims 5-9, and 15 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to point out and distinctly claim the subject matter which the applicant regards as the invention. (OA, p. 4-5) In original claims 5 and 7 there was a typographical error wherein "z219c" was mistakenly written as "z219a." As the instant claims to not have reference to the named polypeptide, z219c, these errors are no longer in the claims. Applicant believes that the instant claims point out and distinctly claim the subject matter, as required by 35 U.S.C. §112, second paragraph, and that this rejection should be withdrawn.

Claim 5 was rejected for lacking antecedent basis for "the z219a polypeptide" in claim 4. The reference to "z219a" was deleted and language inserted to clarify that the claim is drawn to "the polynucleotide" that "encodes a polypeptide that consists of a sequence of amino acid residues as shown in SEQ ID NO:2." Instant claim 5 has clear antecedent basis for the language used therein, and points out and distinctly claims the subject matter, as required by 35 U.S.C. §112, second paragraph. Consequently, this rejection should be withdrawn.

Claim 6 was rejected as indefinite because it was "confusing, as it is not clear what structure is claimed and what the motifs are." The specification defines "M1-{25-26}-M2-{15}-M3-{11}-M4-{34-36}-M5," and the motifs included in claim 6 on page 14, line 1, to page 15, line 14. Applicant amended claim 6 to include this language from the specification in the claims, thus rendering the Examiner's concern with indefiniteness moot. Claim 6 points

out and distinctly claims the subject matter, as required by 35 U.S.C. §112, second paragraph. Consequently, this rejection should be withdrawn.

Claim 7 was rejected because it "recites a z219a polypeptide, but it is not clear what the final limitations of the polypeptide are." As there is no explanation, Applicant is not clear what the Office means as "the final limitations of the polypeptide." However, Applicant has amended the claim to omit all language referring to "z219a" from the claim, as the claim is drawn to a DNA segment encoding a polypeptide defined in the claim "as shown in SEQ ID NO:2 from amino acid number 23 (Phe), to amino acid number 223 (Phe)," and the recitation of "z219c" is not necessary. Similarly, newly added claims 22, and dependent claims 23-25 do not include the recitation of "z219c." Instant claim 7, and dependent claims 8, 9 point out and distinctly claim the subject matter, as required by 35 U.S.C. §112, second paragraph. Consequently, this rejection should be withdrawn.

Claims 8, 9, and 15 were rejected under 35 U.S.C. §112, second paragraph as being indefinite for failing to point out and distinctly claim the subject matter which the applicant regards as the invention. (OA, p. 7) However, the Office has supplied no reason therefor, and hence has not met the requisite burden of proof to provide a *prima facie* case of indefiniteness. However, to simplify matters Applicant has canceled claim 15, and re-written it as claim 25 omitting all language referring to "z219c," as the recitation of "z219c" is not necessary therein. Instant claim 25 points out and distinctly claims the subject matter, as required by 35 U.S.C. §112, second paragraph. Consequently, this rejection of claims 8 and 9 should be withdrawn as it may be applied to newly added claim 25.

In view of the amendment and remarks above, Applicant respectfully requests that the rejection of claims 5-9 and as it may apply to claim 25 under 35 U.S.C. §112, Second Paragraph, be properly withdrawn.

(2) Rejection of claims 1-9, and 15 under 35 U.S.C. §101

Claims 1-9 and 15 were rejected under 35 U.S.C. §101 because the claimed invention "is not supported by either a specific asserted utility or well established utility." (OA, p. 5-6) Claim 15 was canceled, and re-written as claim 25 to provide proper

dependency. Applicant respectfully traverses this rejection as it applies to claims 1-9, and as it may apply to newly added claims 22-25.

To be considered useful under 35 U.S.C. §101, an invention must have a specific, substantial and credible utility. It is well established "when a properly claimed invention meets at least one stated objective, utility under §101 is clearly shown." (*Raytheon Co. v. Roper Corp.*, 724 F.2d 951, 958 (CAFC 1983)). That is, only a single utility for an invention needs be disclosed in a patent application to satisfy the 35 U.S.C. §101 utility requirement. Moreover, Section II.B.2(a) of the "Revised Utility Examination Guidelines" state "An invention has a well-established utility if a person of ordinary skill would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., properties...)" (64 FR 244, p. 71441) The Office states that "[t]he specification sets forth various utilities for the claimed nucleic acid and encoded protein; however none are specific to the nucleic acid claimed." (OA, p. 6) Applicant respectfully disagrees with this contention as the specification has indeed asserted at least one specific utility for the claimed polynucleotides. As detailed below, amongst other utilities (e.g., tissue-specific marker), one of skill in the art upon reading the specification would immediately appreciate that the polynucleotides of the present invention are located at a specific chromosomal location associated with human disease, and would immediately appreciate that the polynucleotides could serve as a useful diagnostic for detecting and analyzing translocations and other genetic abnormalities at that locus. As such, one of skill in the art would immediately appreciate that the polynucleotides of the present invention have specific and well-established utility.

The instant claims are drawn to polynucleotides of the present invention. As disclosed in the specification, from page 71, line 33 to page 74, line 7, the polynucleotides of the present invention can serve as diagnostics for human chromosome 3 abnormalities, particularly at the specific locus where the z219c gene is located, 3p21.1-p13. As further disclosed in the specification and known by one of skill in the art, applicant emphasizes that translocation and loss of heterogeneity at the specific 3p21.1-p13 locus is clearly associated with human disease, such as cancers (e.g., see page 73, lines 7-35, and references provided),

and hence the polynucleotides of the present invention can be used specifically as a diagnostic. Contrary to the beliefs of the Office, Applicant has indeed asserted a specific utility for the claimed polynucleotides of the present invention. Moreover, it is well settled in the art how to use such polynucleotides as probes to detect and analyze chromosomal aberrations in the 3p21.1-p13 region of chromosome 3 is discussed and enabled in the specification (page 71, line 33 to page 74, line 7). Moreover, said utility is substantial and credible, as it is well known in the art that diagnostics for genetic diseases and tumors are sought after, and they are currently used in present day medicine to diagnose genetic disease or malignancy, or carriers or those susceptible to genetic disease, or to assist physicians in analyzing disease.

Moreover, one of skill in the art would at the time of filing would recognize that chromosomal abnormalities such as translocations and loss in the 3p21.1-p13 locus would be and are evident in many human tumors, and that this locus of chromosome 3 is a hot-spot wherein translocations and LOH within 3p21.1-p13 are evident in tumors and malignancy in humans. Hence z219a polynucleotide probes can serve as a diagnostic for such chromosomal aberrations (as described in the specification page 71, line 33 to page 74, line 7), and aid in diagnosis of human cancers. Moreover, one of skill in the art would recognize that of z219c polynucleotide probes are particularly useful for diagnosis of gross chromosomal abnormalities associated with loss of heterogeneity (LOH), translocation, rearrangements, chromosome gain (e.g. trisomy), DNA amplification, and the like. Such uses for the polynucleotides of the present invention are described in the specification (page 72 lines 12-30). Translocations, deletions and LOH within chromosomal locus 3q21.1-p13 wherein the z219c gene is located were known at the time of filing to be associated with human disease, and research has continued to show that this locus is involved in human disease. Upon reading the specification, these uses would be apparent to one of skill in the art. For example:

> The z219c gene is located at the 3p21.1-p13 region of chromosome 3. ... For example, arginine-rich protein (ARP) maps to 3p21.1. Deletions in ARP are associated with solid tumors of various types, and deletions and mutations at codon 50 are observed in pancreatic tumors (Shridhar, R. et al, Cancer Res., 56:5576-5578, 1996; Shridhar, V. et al, Oncogene, 12:1931-1939, 1996; Shridhar, V. et al, Oncogene, 14:2213-2216, 1997). Moreover, z219c polynucleotide probes can be used to detect abnormalities or genotypes associated with these ARP defects. ... familial nonpolyposis type 2 colorectal

cancer (3p21.3), and Larsen syndrome (3p21.1-p14.1)... (see, specification, page 73, line 7-17, and 24-25)

LOH and translocations within 3q21.1-p13 are associated with several human cancers and hence z219c polynucleotides within this locus are useful. As discussed in the specification on page 73 lines 7-17, deletions in ARP (3p21.1) are associated with solid tumors of various types. Shridhar, V. et al, Oncogene, 12:1931-1939, 1996, cited in the specification, show that chromosome 3p breakage, translocation and LOH at 3p14 is common in renal cell carcinomas, including nonpapillary, papillary and oncocytomas. Moreover, other aberrations within 3q21.1-p13 are associated with cancers, for example: mylodysplastic syndrome and acute myeloid leukemia (3p21 is recurrent treatment-related breakpoint, Shi, G et al,. Cytogenet. Cell Genet. 74:295-299, 1996); human carcinomas (3p21.3 LOH, Imreh, S et al. Genes Chromosomes Cancer 20:224-233, 1997); hereditary renal cell carcinoma (3p14 translocation breakpoint and loss, Shridhar, R. et al, Cancer Res., 56:5576-5578, 1996 cited in specification); malignant development to clear cell or nonpapillary renal cell carcinoma (losses of 3p21 necessary, Vand den Berg, A et al., Genes Chromosomes Cancer. 15:64-72, 1996, Vand den Berg, A, and Buys, CH Genes Chromosomes Cancer. 19:59-76, 1997); human lymphoid neoplasms (3p21 breakpoints and deletions, Cigudosa, JC et al. Genes Chromosomes Cancer. 25:123-133, 1999); renal cell carcinoma (3p12-14 translocation and 3p21.2-21.3 deletion, Clifford, SC et al. Genes Chromosomes Cancer. 22:200-209, 1998); malignant lymphomas ((3;11)(p21;q23) translocation; Diabata, M. et al. Cancer Genet. Cytogenet. 117:28-31, 2000). Copies of the references above are provided for the Examiner's convenience. It is clear, and it would have been at the time of filing, that the 3q21.1-p13 locus would be immediately appreciated by one of skill in the art as a critical region for translocations involved in human malignancies and tumors. As such, one of skill would immediately appreciate that polynucleotide probes as markers within this locus, such as the z219c polynucleotides of the present invention, are useful for detecting and analyzing translocations and LOH involved in human malignancies and tumors.

Thus, since the z219c gene maps to this critical region involved in human malignancy and tumors, z219c polynucleotide probes of the present invention can be used to

detect abnormalities or genotypes associated with 3q21.1-p13 translocation, deletion LOH, and the like, described above. In addition, and described in part A(3)(b) below, Applicant emphasizes that such uses of the inventive *polynucleotides* are independent of the use or function of the z219c polypeptide. These uses of the polynucleotides of the present invention for a diagnostic for chromosome aberrations at the 3q21.1-p13 locus, e.g., in cancers, do not apply to polynucleotides generally, but are specific of the z219c polynucleotides of the present invention. Moreover, the specific utility of z219c polynucleotides to detect such chromosomal aberrations is clearly described in the specification at pages page 71, line 33 to page 74, line 7 and more specifically at. 72 line 12-30. Moreover, this utility is well-established, as one of ordinary skill would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., because of the property of these polynucleotides having a 3q21.1-p13 chromosomal localization).

Claims 1-9 and 22-25 are indeed supported by a specific asserted utility that is substantial and credible. This is all 35 U.S.C. §101 requires. Consequently, the rejection of claims 1-9 and as it may apply to claims 22-25 should be properly withdrawn.

(3) Rejection of claims 1-10 and 15 under 35 U.S.C. §112, First Paragraph

(a) Rejection of claims 1-10 and 15 under 35 U.S.C. §112, First Paragraph

Claims 1-9 and 15 were rejected under 35 U.S.C. §112, First Paragraph because "since the claimed invention is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art would not know how to use the claimed invention." (OA, p. 7). Claim 15 was canceled, and re-written as claim 25 to provide proper dependency. Applicant respectfully traverses this rejection as it applies to claims 1-9, and as it may apply to newly added claims 22-25.

As discussed in Part A(2) above, Applicant has indeed asserted a specific and well established utility for the claimed polynucleotides. Claims 1-9 and 22-25 are indeed supported by a specific and well established utility that is substantial and credible. As such, the Office has no basis for the instant enablement rejection under 35 U.S.C. §112, First Paragraph. Moreover, one of skill in the art would know how to make and use the invention,

and the specification teaches one of skill in the art to do so at page 71, line 33 to page 74, line 7. Consequently, Claims 1-9 and 22-25 are enabled, and the rejection under 35 U.S.C. §112, First Paragraph, should be properly withdrawn.

(b) Rejection of claims 1, 3-10 and 15 under 35 U.S.C. §112, First Paragraph

Claims 1, 3-10 and 15 were rejected under 35 U.S.C. §112, First Paragraph "as containing subject matter which is not described in the specification in such a way as to enable one of skill in the art to which it pertains, or which it is most nearly connected, to make and/or use the invention." (OA, p. 7) Claim 15 was canceled, and re-written as claim 25 to simplify the issues and provide proper dependency. Applicant has amended claim 10, and respectfully traverses this rejection as it applies to instant claims 1-9, and as it may apply to newly added claims 22-25.

In making this rejection of claims 1, 4, 7, and 10, the Office states, in reference to inventive polynucleotides that encode a polypeptide that is "at least 90% identical" to the recited sequences of SEQ ID NO:2:

> As no specific function is provided for the z219c polypeptide, it is unpredictable which amino acids and nucleotides could be modified in order to maintain the function of the protein. In view of the state of the art, of the lack of guidance about which amino acids are essential for the function ... it would constitute undue experimentation to make and use the invention of claims 1, 2-9, and 15. While one of skill in the art would know how to use the predicted signal sequence ... (claim 10), one of skill in the art would not know how to make the claimed invention. ... (OA. P. 7)

First, Applicant believes the Office has mistakenly included independent claim 2 in this rejection as it is drawn to the recited polynucleotide sequence of SEQ ID NO:1 and does not contain "at least 90% identical" language. Moreover, Applicant believes that the instant rejection no longer applies to the instant claim 4, which has been re-written as an independent claim, and does not include "at least 90% identical" language. Hence, claim 4 is drawn to an isolated polynucleotide that encodes a polypeptide comprising the amino acid sequence as shown in SEQ ID NO:2 from amino acid number 23 (Phe), to amino acid number 223 (Phe); or the amino acid sequence as shown in SEQ ID NO:2 from amino acid number 1

(Met), to amino acid number 223 (Phe) (page 14, lines 11-19). The specification clearly describes SEQ ID NO:1, and polynucleotides that encode SEQ ID NO:2 and how one would make and use them (e.g., see part A(2) above, and paragraph below). Moreover, claim 15 was re-written as claim 25 and depends from independent claim 22 rather than claim 7. As such, it no longer depends from a claim containing "at least 90% identical" language, and for the reasons above is enabled along with claims 22-24. Upon reading the specification and claims, one of skill in the art could make and use the polynucleotides of claims 2, 4, and dependent claim 5, and claims 22-25 without undue experimentation. This is all 35 U.S.C. §112, First Paragraph requires. Consequently, the rejection of claims 2, 4, and 5, and as it may apply to claims 22-25, should be properly withdrawn.

Second, the instant claims 1-9, as well as newly added claims 22-25, are drawn to polynucleotides that can be used to detect human chromosomal abnormalities associated with disease, as described in Part A(2). One of skill in the art would recognize that the use of such polynucleotides is independent of the use or function of the polypeptides, or a delineation of which amino acids and nucleotides could be modified in said polypeptide. Although Applicant has chosen to express the polynucleotides of the present invention in terms of SEQ ID NO:2 rather than SEQ ID NO:1, it is the *polynucleotides* that are the object of the instant claims. The specification discloses throughout how one could make and use the polynucleotides of the present invention, for example at page 20, line 21, to page 23, line 7; and page 71, line 33 to page 74, line 7. Moreover, the specification also discloses variant z219c polynucleotides as well as how to determine whether a sequence is "at least 90% identical" to SEQ ID NO:1 or SEQ ID NO:2, without undue experimentation (see specification, for example, at page 23, line 5, to page 27, line 4). Moreover, one of skill in the art can readily determine whether a polynucleotide falls within the claims; as an illustration, one of skill in the art with little if any experimentation could commonly use a computer program, such as FASTA, to determine whether a sequence is "at least 90% identical" to e.g., SEQ ID NO:1 or SEQ ID NO:2. Moreover, It is well known in the art that a polynucleotide of the present invention would not have to be 100% identical in sequence to SEQ ID NO:1 (or a

polynucleotide sequence encoding SEQ ID NO:2) to serve as a probe to hybridize to a target sequence, e.g., human chromosomal DNA at locus 3p21.1-p13, since degenerate sequences and polynucleotide probes are commonly used to hybridize to, isolate and identify non-identical polynucleotide sequences such as allelic variants, and orthologs (e.g., see, page 15, line 32 to page 20, line 20; and page 22 line 12 to page 26, line 3), and DNA fragments or PCR are often used to probe chromosomes and determine chromosomal localization (e.g., see, page 71, line 33 to page 74, line 7, and Example 3). That is, one of skill in the art would have a reasonable expectation of success that the polynucleotides of the present invention that encode a polypeptide that is at least 90% identical to SEQ ID NO:2 could be used detect human chromosomal abnormalities associated with disease, as described in Part A(2). In addition, expression vectors and cultured cells (e.g., claims 7-9 and 22-24) are routinely used in the art to generate copies or provide templates of the polynucleotide sequences of the present invention, e.g., to be subsequently isolated as polynucleotide probes. Again, Applicant emphasizes that these *polynucleotide* inventions are independent of the use or function of the z219c polypeptide. As such, Applicant fails to see the relevance or scientific basis for The Office's requirement for determining the function of z219c polypeptide, or describing which amino acids and nucleotides could be modified in said polypeptide, in order to make and use the polynucleotides of the present invention. Upon reading the specification and claims, one of skill in the art can make and use polynucleotides of the present invention, without undue experimentation. This is all 35 USC 112, First Paragraph, requires. Consequently, the rejection of claims 1-9 and as it may apply to claims 22-25, should be properly withdrawn.

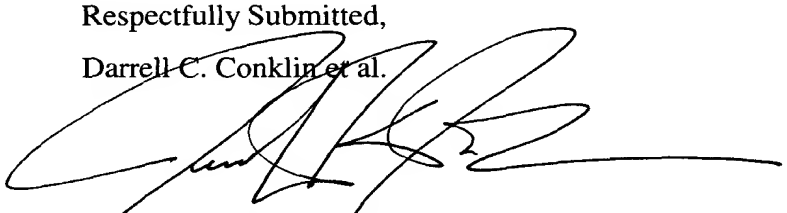
Finally, Applicant agrees with the Office that one of skill in the art would know how to use the predicted signal sequence of claim 10. However, regarding enablement of claim 10, in addition to a concern about the "at least 90% identical" limitation, the Office states "While one of skill in the art would know how to use the predicted signal sequence ... (claim 10), one of skill in the art would not know how to make the claimed invention, and how to use a polypeptide 90% identical to the signal peptide that is not functional.." To simplify matters, Applicant has removed the "at least 90% identical" limitation from claim 10 without

prejudice to the prosecution of the subject matter in a subsequent application. Instant claim 10 is drawn to a DNA construct encoding a fusion protein, the DNA construct comprising: a first DNA segment encoding a polypeptide comprising a sequence of amino acid residues 1 (Met) through 21 (Met) of SEQ ID NO:2; and a second DNA segment encoding an additional polypeptide, wherein the first and second DNA segments are connected in-frame; and encode the fusion protein. Support is shown at page 3, line 26-33; and page 33, line 33, to page 35, line 12. The DNA construct here encodes a fusion protein that uses the z219c signal polypeptide (residue 1 (Met) to residues 21 (Met) of SEQ ID NO:2) to direct other polypeptides, such as non-secreted proteins, into the secretory pathway (page 33, line 32, to page 34, line 15). One of skill in the art would recognize, that the second DNA segment encoding an additional polypeptide could be a DNA segment encoding any additional polypeptide to be secreted via the z219c signal peptide. It is well known, using molecular biology techniques how to connect DNA constructs in-frame to produce a fusion protein (see, e.g., Sambrook et al., Molecular Cloning: A Laboratory Manual, 2nd ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989, and Ausubel et al., eds., Current Protocols in Molecular Biology, John Wiley and Sons, Inc., NY, 1987; both incorporated by reference and cited throughout the specification). Upon reading the specification and claims, one of skill in the art can make and use polynucleotides of the present invention, without undue experimentation. This is all 35 USC §112, First Paragraph, requires. Consequently, the rejection of claim 10 should be properly withdrawn.

In view of the amendment and remarks above, Applicant respectfully requests that the rejection of claims 1-10 and as it may apply to claims 22-25 under 35 U.S.C. §112, First Paragraph, be properly withdrawn.

Early reconsideration and allowance of the pending claims is respectfully requested. If the Patent Examiner believes that a telephone interview would expedite prosecution of this patent application, please call the undersigned at (206) 442-6676.

Respectfully Submitted,
Darrell C. Conklin et al.



Jennifer K. Johnson, J.D.
Registration No. 43,696

Enclosures:

Amendment Fee Transmittal (in duplicate)
Postcard
Appendix of amended claims (4 pages)
Copies of 9 references